Scientific Abstract

HIV-1 infection causes progressive depletion of CD4+ T lymphocytes and, after a period of clinical latency averaging 7-12 years, the clinical syndrome of AIDS in the overwhelming majority of patients. The gravity of the expanding pandemic and lack of effective treatments continue to spur a search for innovative therapies. Ribozymes are potentially therapeutic RNA molecules that contain anti-sense sequences for specific recognition, and RNA-cleaving enzymatic activity (11-20). We have shown that human T-cell lines and primary peripheral blood human T cells transduced with a hairpin ribozyme that cleaves HIV-1 RNA in the 5' leader sequence are intracellularly immunized against challenge with cloned and uncloned HIV-1 isolates (7,8,9). Escape or resistant virus is not detected after long term culture. The transduced T cells persistently express the ribozyme and there are no apparent deleterious effects on cell proliferation or long-term viability (9). The ribozyme acts at two steps in the viral lifecycle: by cleaving both afferent viral RNA genomes (9) and efferent viral mRNA expressed from integrated provirus (7,8,9). In this study, we will evaluate the safety and efficacy of ribozyme gene therapy in four to six patients with HIV-1 infection by reinfusing autologous CD4+ T cells that have been transduced *ex vivo* with a retroviral vector that expresses the HIV-1 leader sequence ribozyme. The *in vivo* kinetics and survival of ribozyme-transduced cells will be compared by limiting dilution PCR with those of a separate aliquot of cells transduced with a control vector (identical except for the ribozyme cassette). The level and persistence of ribozyme expression will also be assessed. The results will determine whether this ribozyme can protect CD4+ T cells in patients with HIV infection and will aid design of future trials of larger scale T cell replacement therapy and trials of hematopoietic stem cell gene therapy for HIV disease.